Evaluation of Cardiovascular Autonomic Functions in patients with Transient Ischemic Attack

Original Research Article

ISSN : 2456-1045 (Online)
(ICV-MDS/Impact Value): 63.78
(GIF) Impact Factor: 4.126
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Journal Code: ARJMD/MDS/V-32.0/I-1/C-13/DEC-2018
Category : MEDICAL SCIENCE
Volume: 32.0 /**Chapter**- XIII / **Issue**-1(DECEMBER-2018)
Journal Website: www.journalresearchijf.com
Paper Received: 31.12.2018
Paper Accepted: 07.01.2019
Date of Publication: 17-01-2019
Page: 74-78

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Citation of the Article

Chaswal M. ; Kaul B. ; Kapoor R. ; Ahluwalia H. ; Prakash G. (2018) Evaluation of cardiovascular autonomic functions in patients with transient ischemic attack ; *Advance Research Journal of Multidisciplinary Discoveries.32(13)pp. 74-78*

ABSTRACT

Background & Objective: Cardiac autonomic dysfunction is commonly observed in stroke patients. However little is known about the status of autonomic functions in patients with transient ischemic attack (TIA). The study aimed to assess cardiac autonomic functions in TIA patients and controls by cardiovascular reflex tests and analysis of short term heart rate variability (HRV).

Methods: 26 TIA patients and 27 age and sex matched controls were included. Autonomic reactivity was assessed by using tests of autonomic cardiovascular reflexes such as deep breathing test (DBT) and lying to standing test (LST). Measurement of HRV included both time and frequency domain parameters. In the time domain we estimated standard deviation of normal R-R intervals (SDNN) and square root of the mean squared differences of successive R-R intervals (RMSSD). Frequency domain analysis included estimation of total power (TP), high frequency (HF) power, low frequency (LF) power and LF to HF ratio.

Results: Compared with controls, HRV components including SDNN, RMSSD, TP, HF power were reduced and LF power, LF to HF ratio significantly increased in patients with TIA. A significant decrease of parasympathetic reactivity was also observed in TIA patients compared to controls.

Conclusion: TIA patients have autonomic imbalance suggestive of attenuated parasympathetic influence and heightened sympathetic response. Autonomic dysregulation may predispose TIA patients to an increased risk of recurrent TIA and future stroke.

KEYWORDS:

Transient ischemic attack, stroke, autonomic functions, heart rate variability, cardiovascular reflex tests

I. INTRODUCTION

Transient ischemic attack (TIA) or mini-stroke has been defined as brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction. [1] TIAs are often neglected because symptoms tend to improve. However, TIA is an important predictor and warning sign of a possible future stroke. In people who have a TIA, the incidence of subsequent stroke is as high as 11% over the next 7 days and 24-29% over the following 5 years. [2] As stroke is the second commonest cause of death and a leading cause of long term disability worldwide, [3] therefore it is vital that TIA is treated seriously and as early as possible. The pathophysiology of TIA is still unclear and considered multi-factorial, with the autonomic nervous system likely playing an important part. Though autonomic functions have been studied extensively in stroke patients but there is scarcity of scientific data about status of autonomic functions among patients with TIA. Besides previous studies on autonomic functions in patients with stroke have shown conflicting results. Some reported parasympathetic deficit with hyperactivity of sympathetic nervous system in stroke patients, [4] whereas others have demonstrated suppression of sympathetic responses in these patients.[5] In addition, autonomic dysfunction has been found to be associated with adverse clinical outcome in stroke survivors. [6,7] Given the similarities in the pathogenesis of stroke and TIA, we hypothesized that abnormal autonomic functions would be more common and more frequently impaired, in patients with TIA when compared with controls. This study was therefore undertaken to explore and validate status of sympathetic and parasympathetic division of autonomic nervous system in TIA patients and compare it with controls. Cardiac autonomic function testing included measurement of both autonomic tone as well as reactivity. Autonomic tone was assessed using time and frequency domain components of heart rate variability (HRV). Autonomic reactivity was measured using cardiovascular reflex tests such as deep breathing test (DBT) and lying to standing test (LST).

II. MATERIALS AND METHODS

We recruited 30 patients of TIA from Neurology outpatient department of VMMC and Safdarjung Hospital, New Delhi. However, we were able to record data in 26 patients only, as 4 patients reported discomfort while testing and thus could not complete the testing protocol. Mean age of TIA patients (17 males, 9 females) was 50.35 ± 8.57 years. These patients were those with a history of one TIA with symptoms subsiding in less than 24 hours. Since, TIA has a complex spectrum of comorbidities, of the 26 patients, 10 had a history of hypertension, 5 had a history of type 2 diabetes and 1 patient had hyperchlostremia. However, those patients requiring treatment with effects on autonomic functions were excluded. Patients with arrhythmia, uncontrolled hypertension, uncontrolled diabetes mellitus, impaired renal function, ischemic heart disease, thyroid disorder, connective tissue disorder or other conditions associated with autonomic dysfunction, smokers and alcoholics were also excluded from the study. 27 control participants age and gender matched were recruited from among family members, friends of recruited patients and from those attending OPD for minor complaints. They had no previous history of TIA or stroke. However, we ensured that control group matched the TIA group for comorbid conditions. The study was launched after getting ethical clearance from Institutional Ethical Committee of VMMC and Safdarjung Hospital, New Delhi, India.

All subjects were included in this study after written informed consent had been obtained. The subjects were required to respond to a detailed clinical performa and a complete general physical and neurological examination of all participants was done on the day of testing. The anthropometric measurements included height (cms), weight (kg) and body mass index (kg/m^2).

Assessment of autonomic functions: In all subjects, autonomic function testing was done by autonomic cardiovascular reflex tests for assessment of autonomic reactivity and by analysis of short term HRV for assessment of autonomic tone. For evaluation of sympathetic reactivity we measured change in systolic blood pressure in response to standing, whereas parasympathetic reactivity was assessed by heart rate response to deep breathing (delta heart rate, Expiration: Inspiration ratio) and to standing (30:15 ratio). Testing was performed in a warm, quiet room, in the forenoon after familiarizing the subjects with the testing procedure. Subjects were asked to refrain from caffeine ingestion on the day of the investigation and to take only light breakfast at least 2 hours prior to testing. The subjects were asked to lie comfortably for 15 minutes and their resting blood pressure (BP) and heart rate (HR) were recorded. BP was monitored by aneroid sphygmomanometer at intervals throughout the test. Monitoring of the HR and respiration during the test was done by recording electrocardiogram (ECG) and stethographic respiratory tracings on student physiograph (Recorders and Medicare, Chandigarh, India) respectively.

Protocol of tests :

Deep breathing test (DBT) - The patient sat quietly and was instructed to breathe smoothly and deeply at 6 breath/min. (5 seconds inspiration and 5 seconds expiration). HR was measured from ECG. Delta heart rate (ΔHR) was the difference between maximal and minimal HR during inspiration and expiration, averaged for 6 cycles. Expiration: inspiration (E: I ratio) was the ratio of longest R-R interval and shortest R-R interval, averaged over 6 cycles. [8]

Lying to standing test (LST) - The BP and the ECG were recorded in supine position. Then the patient was told to stand within 3 seconds and BP was recorded at 0.5th, 1st, 2nd, 2.5th and 5th minute after standing. ECG was also continuously recorded during the procedure. 30:15 ratio was calculated as the ratio between longest R-R interval at or around the 30th beat and shortest R-R interval at or around the 15th beat. The change in systolic blood pressure (SBP) on standing was recorded as the difference between SBP at rest and lowest SBP after standing. [9]

Heart Rate Variability (HRV) measurement - HRV was measured according to the Guidelines laid down by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. [10] The study subject was asked to lie down comfortably. The ECG recording for 5 minutes was taken in the Lead II configuration using the Power lab data acquisition system, AD instruments. As per the standard recommendation, the sampling rate was kept at 500 Hz. The analysis of the detected R-R waveform was carried out in time domain and frequency domain. Time domain measures included standard deviation of normal R-R intervals (SDNN), and square root of the mean squared differences of successive R-R intervals (RMSSD). SDNN reflects all the cyclic components responsible for variability in the period of recording whereas RMSSD indicates vagally mediated modulation of heart rate. Frequency domain parameters of HRV were calculated using Fast Fourier Transform (FFT) in order to derive the spectral power density of the different component frequencies in the heart rate. A Hanning window was used to attenuate spectral leakage and the power spectrum was subsequently divided into three frequency bands: very low frequency (VLF) – (0.001 to 0.04) Hz, low frequency (LF) – (0.04 to 0.15) Hz, and high frequency (HF) – (0.15 to 0.4) Hz. Sympathovagal balance was determined by LF to HF ratio (LF: HF). The power spectral densities were plotted in ms^2. The LF and HF power were also reported in normalized units, which represent the relative value of each power in proportion to the total power minus the VLF component. The normalised units minimize the effect of changes in total power on the value of HF and LF spectral components. The HF component of the power spectrum modulated by respiration reflects primarily parasympathetic activity, whilst the LF component represents a mixture of vagal and sympathetic influences. [10]

III. STATISTICAL ANALYSIS

Statistical analysis was performed by the SPSS program for Windows, version 17.0(SPSS, Chicago, Illinois). Continuous variables are presented as mean ± SD and categorical variables are presented as absolute numbers and percentage. Data were checked for normality before statistical analysis. Normally distributed continuous variables were compared using the unpaired t test, whereas the Mann-Whitney U test was used for those variables that were not normally distributed. Categorical variables were analyzed using either the chi square test or Fisher's exact test. $p < 0.05$ was considered statistically significant.

IV. RESULTS

Table 1 shows the demographic and baseline cardiovascular parameters of two groups. The mean age of TIA subjects was 50.35 ± 8.57 years and that of control subjects 49.33 ± 8.03 years. There was no significant difference between the two groups with respect to age, gender distribution, body mass index and history of hypertension, diabetes mellitus, hypercholestremia. In the TIA group, relative to controls, baseline systolic blood pressure (SBP) and diastolic blood pressure (DBP) were higher (p=0.072 and p=0.062, respectively) but the difference was not statistically significant.

Table1: Comparison of baseline characteristics between TIA patients and controls

Variable	Patients (n=26)	Controls(n=27)	p value
Age (years)	50.35 ± 8.57	49.33 ± 8.03	0.659
Gender Males n (%) **Females n (%)**	17 (65.4%) 9 (34.6%)	17 (63.0%) 10 (37.0%)	0.854
Height (cm)	166.63 ± 7.62	168.12 ± 9.04	0.522
Weight(kg)	69.07 ± 11.65	70.69 ± 12.21	0.623
Body mass index(kg/m^2)	24.82 ± 3.51	24.95 ± 3.38	0.894
History n (%)			
Diabetes	5(19.2%)	3(11.1%)	0.409
Hypertension	10(38.5%)	8(29.6%)	0.569
Hypercholestremia	1(3.8%)	1(3.7%)	1.000
SBP(mmHg)	136.5 ± 12.34	128.0 ± 15.86	0.0721
DBP(mmHg)	83.27 ± 9.27	78.26 ± 9.83	0.0621
Heart rate(beats/min)	75.81 ± 11.59	75.19 ± 9.07	0.828

Values are expressed as n (%) or mean ± standard deviation; n: number of subjects; SBP: systolic blood pressure; DBP: diastolic blood pressure; $p < 0.05$ statistically significant.

Table 2 depicts both time domain and frequency domain parameters of HRV. In time domain, the TIA group had lower values of SDNN and RMSSD when compared to control group (p=0.026 and $p < 0.001$, respectively). In frequency domain, the TIA group showed a significant decrease in total spectral power ($p < 0.001$). LF component in absolute units of the TIA patients differed insignificantly (p =0.093) from LF of the control subjects, whereas the same calculated as normalized units was found to be significantly higher in TIA patients (p=0.006). The HF (in absolute units) was significantly low in TIA patients ($p < 0.001$) as compared to the HF (absolute units) of controls. Similar trend was observed in the normalized units of HF (p=0.016). The LF/HF ratio, which is thought to express the sympathetic versus parasympathetic balance was higher in TIA patients compared with controls (p=0.004).

Table 2: Heart rate variability in the time and frequency domain in TIA patients and controls

Parameters	Patients (n=26)	Controls (n=27)	p value
SDNN(ms)	30.90 ± 11.94	39.47 ± 11.68	0.026
RMSSD(ms)	21.14 ± 11.53	35.31 ± 14.02	<0.001
Total power(ms^2)	883.63 ± 625.21	1680 ± 1057.95	<0.001
LF power (ms^2)	233.90 ± 176.49	385.34 ± 375.66	0.093
LF(nu)	54.71 ± 19.59	41.97 ± 12.68	0.006
HF power (ms^2)	179.84 ± 198.44	449.73 ± 397.48	<0.001
HF (nu)	36.16 ± 17.50	46.90 ± 12.86	0.016
LF /HF ratio	2.11 ± 1.49	1.04 ± 0.67	0.004

Values are expressed as mean ± standard deviation; n- number of subjects; SDNN- standard deviation of normal R-R intervals; RMSSD- square root of the mean squared differences of successive R-R intervals; LF- low frequency; HF- high frequency; nu- normalized unit; $p < 0.05$ statistically significant.

On comparison of sympathetic reactivity (Table 3), in lying to standing test, the average fall in SBP was more in TIA patients(p=0.006). For the tests of parasympathetic reactivity, the delta heart rate, E:I ratio and 30:15 ratio in controls were significantly higher compared to TIA patients ($p < 0.001$, p=0.002 and p=0.007, respectively).

Table 3: Cardiovascular reflex tests in TIA patients and controls

Test	Parameters	Patients (n=26)	Controls (n=27)	p value
Sympathetic reactivity				
Lying-to -standing test	Average fall in systolic blood pressure (mmHg)	6.54 ± 6.88	1.59 ± 2.78	0.006
Parasympathetic reactivity				
Lying –to- standing test	30:15 ratio	1.18 ± 0.17	1.92 ± 3.22	0.004
Deep breathing test	Delta heart rate (bpm)	12.98 ± 5.71	19.91 ± 6.65	<0.001
	Expiration:Inspiration ratio	1.21 ± 0.12	1.32 ± 0.13	0.002

Values are expressed as mean ± standard deviation; n- number of subjects; 30:15 ratio- immediate heart rate response to standing; $p < 0.05$ statistically significant.

V. DISCUSSION

To the best of our knowledge this is the first study of comprehensive assessment of autonomic functions in patients of TIA in comparison with controls. The findings based on reliable and sensitive cardiac autonomic tests, indicate autonomic dysfunction suggestive of sympathetic predominance and suppression of parasympathetic activity in patients of TIA.

In the present study, time domain analysis of HRV revealed a decrease in SDNN, an index of overall variability and RMSSD, a measure of vagal tone in TIA patients. Amongst frequency domain parameters, total power, a measure of total variance of HRV and HF, a measure of vagal activity showed significantly lower values, whereas there was increase in LFnu and LF: HF ratio in TIA patients compared to controls. For the reflex tests, a significant decrease in HR variation with deep breathing ie. E:I ratio and delta HR as well as a decrease in HR response to standing(30:15 ratio) was observed in TIA patients compared to controls. Together these findings suggest autonomic dysfunction in the form of increased sympathetic activity associated with concurrent parasympathetic hypofunction in TIA patients, who had completely recovered from the ischemic episode and had no residual neurological deficit.

Disturbances of autonomic cardiovascular regulation have been frequently encountered in stroke. [11, 12] However, there is paucity of studies about status of autonomic cardiovascular regulation in TIA and the results are contradictory. In study by Zhang et al. patients with TIA and minor stroke were found to have similar autonomic nervous system function when compared with controls. [13] However, another study reported a significant decrease in VLF, LF and HF in patients of TIA or minor stroke. [14] Contrary findings in prior studies could be due to difference in methodology.

In our study, there was no difference between controls and TIA group with regard to the history of hypertension, diabetes and hypercholestremia. The body mass index was also comparable in the two groups and we excluded all diseases that may affect HRV in studied subjects. Besides this, statistical analysis has considered variations due to differences in medications among participants. All these considerations make the effects of possible confounding factors on autonomic modulation unlikely in this study. Thus it may be said that the observed changes in autonomic functions are due to TIA itself.

Existence of extremely limited datasets on the autonomic changes after TIA is a reflection of the fact that TIA is difficult to diagnose and it is often missed as the symptoms tend to improve. However, TIA though commonly referred to as mini- stroke, is a major warning sign of a future stroke and approximately 15% of diagnosed strokes are preceded by TIAs. [15] So it will not be wrong to say that diagnosing a TIA identifies a patient who is at risk for subsequent stroke. Therefore, a better understanding of pathophysiological mechanisms involved in TIA is needed to improve our ability to treat this condition and prevent stroke. From our study it is difficult to comment on the mechanism of autonomic changes seen in TIA, but we may speculate on the basis of previous findings. Atherosclerosis affecting cerebral arteries and arterioles plays a key role in the pathogenesis of stroke as well as TIA. [16] In addition, studies in the past show a close association between autonomic dysfunction and progression of atherosclerosis. [17] Evidence in favor of close association between ischemia as a result of atherosclerotic plaque and autonomic nerve activity are also reported for coronary artery disease and it is known that sympathetic activation may precipitate ischemia and ischemia may lead to neurohormonal activation with increased release of noradrenaline from cardiac sympathetic nerves, thus setting the scene for a vicious circle [18] and this fact is likely to be appropriate for TIA as well. However, irrespective of mechanism, existence of autonomic imbalance in the form of increased sympathetic outflow combined with a decreased parasympathetic activity may be detrimental in patients of TIA. One of possible explanation for this is that activation of parasympathetic nervous system is found to increase cerebral blood flow, improve neurogenesis and serves neuroprotective in addition to anti-inflammatory effects on the central nervous system. [19] Therefore, we may speculate that attenuated parasympathetic tone as well as reactivity, as observed in our study may predispose to or cause stroke in TIA patients. Therefore, TIA is not a mini stroke but it is warning stroke and for preventing strokes, the TIA should be diagnosed correctly and treated seriously and as early as possible.

We do accept limitation of our study in the form of relatively small sample size. Designing a study with a larger sample size will be more informative. Inclusion of other tests like measurement of sympathetic nerve activity and estimation of plasma catecholamines will prove to be more reliable indicators to support our findings.

In conclusion, the data from the present study demonstrated that TIA patients had increased sympathetic activity with concomitant parasympathetic deficiency. However, further studies are required for a detailed understanding of underlying pathophysiological and molecular mechanisms after TIA so as to facilitate the implementation of effective preventive and therapeutic strategies to rectify the autonomic imbalance and improve the outcome of TIA.

VI. ACKNOWLEDGEMENTS

The authors would like to thank Lab technicians Mr. Jhanak Lal Sahu and Mr. Susheel Kumar for their excellent technical assistance. We also thank Mr. Sanjeev and Mr. Shyam Singh for assisting in recruitment.

VII. DISCLOSURE

Conflict of interest: None
Sources of funding: None

REFERENCES

[1]. **Albers GW, Caplan LR, Easton JD, et al.** Transient ischemic attack- proposal for a new definition. N Engl J Med, 2002; 347(21):1713-6.

[2]. **Giles MF, Rothwell PM.** Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol, 2007; 6(12):1063-72.

[3]. **Dorrance AM, Fink G.** Effects of stroke on the autonomic nervous system. Compr Physiol, 2015; 5(3):1241-63.

[4]. **Dütsch M, Burger M, Dörfler C, et al.** Cardiovascular autonomic function in poststroke patients. Neurology, 2007; 69(24): 2249-55.

[5]. **Linden D, Berlit P.** Sympathetic skin responses (SSRs) in monofocal brain lesions: topographical aspects of central sympathetic pathways. Acta Neurol Scand, 1995; 91(5): 372-376.

[6]. **Naver HK, Blomstrand C, Wallin BG.** Reduced heart rate variability after right-sided stroke. Stroke, 1996; 27(2):247-51.

[7]. **Korpelainen JT, Sotaniemi KA, Myllylä VV.** Autonomic nervous system disorders in stroke. Clin Auton Res, 1999; 9(6):325-33.

[8]. **Jyotsna VP, Ambekar S, Singla R, et al.**Cardiac autonomic function in patients with diabetes improves with practice of comprehensive yogic breathing program. Indian J Endocrinol Metab,2013; 17(3): 480–5.

[9]. **Khandelwal E, Jaryal AK, Deepak KK.** Pattern and prevalence of cardiovascular autonomic neuropathy in diabetics visiting a tertiary care referral centre in India. Indian J Physiol Pharmacol, 2011; 55(2):119-27.

[10]. **Heart rate variability:** Standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation, 1996; 93(5):1043–65.

[11]. **Chen CF, Lin HF, Lin RT, et al.** Relationship between ischemic stroke location and autonomic cardiac function. J Clin Neurosci, 2013; 20(3):406–9.

[12]. **Colivicchi F, Bassi A, Santini M, et al.** Cardiac autonomic derangement and arrhythmias in right-sided stroke with insular involvement. Stroke, 2004; 35(9):2094–8.

[13]. **Zhang W, Cadilhac DA, Churilov L, et al.** Does abnormal circadian blood pressure pattern really matter in patients with transient ischemic attack or minor stroke? Stroke, 2014; 45(3):865-7.

[14]. **Chao AC, Chern CM, Kuo TB, et al.** Noninvasive assessment of spontaneous baroreflex sensitivity and heart rate variability in patients with carotid stenosis. Cerebrovasc Dis, 2003; 16(2):151-7.

[15]. **Khare S.** Risk factors of transient ischemic attack: An overview. J Midlife Health, 2016; 7(1):2-7.

[16]. **Coull BM.** Inflammation and stroke. Stroke, 2007; 38(2):631.

[17]. **Huikuri HV, Jokinen V, Syvänne M, et al.** Heart rate variability and progression of coronary atherosclerosis. Arterioscler Thromb Vasc Biol, 1999; 19(8):1979–85.

[18]. **Remme WJ.** The sympathetic nervous system and ischaemic heart disease. Eur Heart J, 1998; 19 (suppl F):F62–71.

[19]. **Cheyuo C, Jacob A, Wu R, et al.** The parasympathetic nervous system in the quest for stroke therapeutics. J Cereb Blood Flow Metab, 2011; 31(5): 1187-95.

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